



UNITED STATES AIR FORCE RESEARCH LABORATORY

MEASUREMENT OF LATE TISSUE DAMAGE IN RHESUS MONKEYS EXPOSED TO PROTONS

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14. ABSTRACT This contract covered studies of the following endpoints in proton-irradiated rhesus monkeys and in age-matched controls: (1) Radiation-accelerated aging of skin fibroblasts in vitro; (2) Wound healing in vivo; (3) Late radiogenic cataracts in rhesus monkeys; (4) Comparative studies of proton-induced cataracts in Fischer-344 rats. (1 & 2) Some deficits in the abilities of monkey skin fibroblasts to perform normal functions in vitro and in vivo were noted following radiation doses slightly higher than those to be expected in space, but it was concluded that following "expected" doses of space radiation, late harmful sequelae will be negligible or undetectable in human skin. (3 & 4) Late cataracts may occur in the ocular lenses of some astronauts exposed to non-lethal space radiations, but the kinetics of radiation cataractogenesis in the rhesus monkey indicate that radiogenic cataracts should not develop until long after the space mission(s) is (are) over. Laboratory rats are not good models for late cataract studies because of their short life spans and the high levels of cataracts that appear naturally in them early in their life span.						
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PREFACE

This contract, titled "MEASUREMENT OF LATE TISSUE DAMAGE IN RHESUS MONKEYS EXPOSED TO PROTONS," covered studies of the following endpoints in proton-irradiated rhesus monkeys and in age-matched controls:

- 1) Radiation-accelerated Aging or Senescence of Skin Fibroblasts *in vitro*
- 2) Wound-healing *in vivo*
- 3) Late Radiogenic Cataracts in Rhesus Monkeys
- 4) Comparative Studies of Proton-induced Cataracts in Fischer-344 Rats

Eighteen publications in peer-reviewed journals and proceedings resulted from and/or were associated with these studies, and thirty-three abstracts were published; one publication is pending (see References), and others are in preparation. This report contains a summary of those results.

INTRODUCTION and HISTORY

The space environment presents hazards from particulate ionizing radiations which are not encountered on the surface of the earth. In 1964, the United States Air Force (USAF) and the National Aeronautics and Space Administration (NASA) initiated a study designed to evaluate late effects of simulated space radiations (primarily energetic protons) in a nonhuman primate model, the rhesus monkey, *Macacca mulatta*. Age-matched control subjects as well as some X-irradiated and electron-exposed primates were included in the experiment. For most of the duration of the experiment the monkeys were housed, cared for and studied at Brooks AFB in San Antonio, TX. The primary endpoints measured in the joint USAF/NASA project were cancers produced by exposures to ionizing radiations.

In addition to the nonhuman primate project, NASA also supported work at Colorado State University on late effects of heavy ions (^{20}Ne , ^{40}Ar and ^{56}Fe) in optic and proximate tissues (including skin and hair follicles) of the New Zealand white rabbit, *Oryctolagus cuniculus*, starting in 1972. Data from those studies on DNA repair in retinal photoreceptors, radiogenic cataracts, wound-healing in vivo and radiation-accelerated in vitro senescence were published in due course, and the research program continued with NASA support through 1996.

Based on the rabbit studies of radiation-accelerated fibroblast senescence *in vitro*, NASA funded a pilot project at Colorado State University to study the same phenomenon in proton-irradiated rhesus monkeys at Brooks AFB. Between 1981 and 1984, techniques for collecting, culturing and transporting monkey fibroblasts were refined by the Colorado State University grantees with the support of the Veterinary Sciences and Radiation Sciences Divisions at the USAF School of Aerospace Medicine at Brooks AFB. In 1985, the USAF funded a contract to Colorado State University to pursue the *in vitro* senescence studies with proton-irradiated monkey skin fibroblasts. In addition, the contractors were tasked to quantify radiogenic cataracts in the monkeys. Results of the studies are summarized here.

RADIATION EFFECTS ON THE SKIN

RADIATION-ACCELERATED SENESCENCE OF SKIN FIBROBLASTS *IN VITRO*

The rabbit studies involved subjects partially irradiated with relatively high doses of heavy ions; the monkey studies involved subjects irradiated "whole-surface" with relatively low doses of energetic (55-MeV) protons which penetrated to a depth of 2.5 cm (1). The radiation doses given the rabbits were high enough so that differences among control and irradiated senescence levels were highly significant. Most of the surviving monkeys studied starting in 1985 had received relatively low or intermediate radiation doses, but the few that had received relatively high doses showed significant differences from controls as far as radiation-accelerated in vitro senescence was concerned (1-3). Results obtained from lower-dose animals were less clear-cut, and were suggestive of trends rather than being statistically significant (1-3, 5, 6).

WOUND HEALING *IN VIVO*

As described above, reference radiation doses to rabbits were generally much higher and to more limited volumes than were the doses to surviving monkeys in these studies. There were trends

among the rates of wound healing in monkeys which indicated some diminution in healing ability in subjects which received relatively low doses, but these were not significantly different statistically from the healing ability exhibited by control subjects (5,6,8).

SKIN STUDIES: CONCLUSIONS

Doses of ionizing radiations slightly higher than those that might be expected in the space environment were shown to cause some changes (deficits) in the ability of skin fibroblasts to proliferate normally *in vivo* and *in vitro*. As far as the abilities of stem cells to perform normal functions following "expected" doses of ionizing radiations in space, however, it was concluded that late harmful sequelae will be negligible or undetectable (1-3, 5, 6, 8).

RADIATION EFFECTS ON THE OCULAR LENS

NORMAL AGING AND RADIOGENIC LENTICULAR OPACIFICATIONS IN MONKEYS

Radiogenic cataracts were noted in irradiated monkeys early in the study, especially among subjects which received relatively high radiation doses, but cataractogenesis was not quantified systematically until 1985. At that time, lenticular opacifications were scored using a well-tried cataract scoring system developed at Colorado State University for radiogenic cataracts in control and irradiated New Zealand white rabbits. Between 1985 and 1995, cataracts were scored in the control and irradiated monkeys at least once, but usually twice, annually. In addition, three medical doctors (ophthalmologists) were called in at different times to observe and quantify lenticular changes in the monkeys. The goals of these consultations were to a) cross-correlate different cataract scoring systems and b) further the progress toward the goal of extrapolating the lens data from the nonhuman primates to humans (see below).

Data from the monkey cataract studies contributed to 13 publications (4-7, 9-15, 17-18), and one publication (16) resulted in part from recalculation of the proton doses to the nonhuman primates' eyes. A fourteenth publication is in preparation at this time.

There were several conclusions regarding late radiogenic cataracts based on data from the Armstrong Laboratory monkey colony alone. These results and their implications are discussed in detail in the articles cited above, but some highlights are listed here.

1) At 20 years post-irradiation with lenticular doses of protons as high as 2.5 Gy, no differences can be detected between cataract scores in control and irradiated monkeys. At 25 years post-irradiation, however, significant differences can be seen between the cataract scores in the same two groups. This indicates that for the endpoint of late radiogenic cataracts, nonhuman primate subjects must be measured for an extended period before conclusions can be drawn about the cataractogenic potential of non-lethal doses of ionizing radiations (see below).

2) Control monkeys do exhibit some measurable senile lenticular cataracts, but those opacifications do not appear until very late in the life spans of the primates. This situation is directly comparable to the human situation (see below).

In addition to scoring radiogenic cataracts in the monkeys at Brooks AFB, contractors traveled twice (using non-USAF sources of funding) to Rijswijk in The Netherlands and measured cataract levels in control and X-irradiated monkeys in a colony there. Comparisons of data from the two colonies was the goal of this part of the study. The Rijswijk monkey colony included subjects which had received whole-body doses of X-rays which would have been lethal had the individuals not been treated with bone-marrow "rescue" protocols. This enabled the investigators to see radiogenic cataracts in relatively high-dose animals (5-8.5 Gy), and allowed us to fill in some blanks in our data base for animals which, in the Brooks AFB colony, were deceased before the systematic measurements of cataracts began in 1985. Also, it was found that old control monkeys in the Rijswijk colony developed senile cataracts at a rate directly comparable to the control monkeys at Brooks AFB. Finally, it was noted that young animals which had received doses of approximately 5 Gy had a latency period of at least 3 years during which time cataract levels different from controls were not apparent; 5 Gy doses caused significant late cataracts in the Brooks AFB monkeys.

Since the ultimate goal of the long-term monkey project is to extrapolate late-effects data to humans for the purpose of making accurate radiation risk estimates, a comparative study was performed using cataract data from humans who had received radiotherapy treatments to their eyes. The study was funded in part by a NASA Specialized Center for Research and Training (NSCORT) grant to Colorado State University and Lawrence Berkeley National Laboratory, and the first publication on this topic appeared in 1994 (15). One of the ophthalmologists associated with that study (W. Meecham, M.D.) has examined the eyes of the Brooks AFB monkeys on two occasions, and also, for comparative and correlation purposes, has inspected the eyes of irradiated rabbits at Colorado State University at least twice.

As part of correlations among subjective and objective scoring systems, a third ophthalmologist (D. Gagliano, M.D.) scored selected Brooks AFB monkeys and compared his system with one objective method now under development at the Massachusetts Institute of Technology (Optical Coherence Tomography or OCT) and a technique under development at Harvard Medical School for quantitating cataracts in human lenses (Lens Opacities Classification System III or LOCS III) as well as with the Colorado State University method of scoring cataracts. Results from this comparative study appear in reference (18).

Based upon the studies summarized above, and upon one preliminary trip to the Radiation Effects Research Foundation (RERF) in Hiroshima, NASA has funded a new project to study medical chart data on senile and radiogenic cataracts among selected survivors from the 1945 blast. This promises to be an enterprise which will a) clarify radiation risk estimates for cataracts and b) aid the survivors in predicting late cataracts from estimated radiation doses.

NORMAL AGING AND RADIOGENIC LENTICULAR OPACIFICATIONS IN RATS

As a supplement to a study designed primarily to observe proton-induced brain tumors in Fischer-344 rats, the contract was modified to allow Colorado State University personnel to measure the development of early, intermediate and late cataracts in rats which received head-only irradiation in 1989. The rats were examined approximately 4 times per year for 2.5 years following lenticular doses of 0, 2, 4, 8.5 or 18 Gray. As expected, the higher doses caused early and intermediate development of significant lenticular opacifications. The 2-Gy dose to the

lenses also caused lenticular opacifications to develop over time, but, although the opacifications appeared slightly earlier in the 2-Gy animals than they did in controls, senile cataracts developed so early in the control rats (starting at 18 months post-irradiation) that they could not be distinguished from 2-Gy cataracts even as late as 29 months post-irradiation (13). The rat cataract study caused us to conclude that, for long-term, late effects studies of radiogenic cataracts, the rat in particular is an unsatisfactory model due not only to its short life span but also to the high level of congenital cataracts in the species.

CATARACT STUDIES: CONCLUSIONS

Late cataracts may be expected to occur in the lenses of some astronauts exposed to non-lethal doses of particulate radiations in space, but the kinetics of radiation cataractogenesis in the rhesus monkey, a nonhuman primate model, are such that radiogenic cataracts should not develop until long after the space mission(s) is(are) over. This conclusion is in contrast to some made by other investigators using rodent models to study the late endpoint of cataract. Laboratory rodents (rats) are not a good model for this particular endpoint because of their short life spans and the high levels of cataracts that appear naturally in these animals relatively early in their life span.

FUTURE STUDIES

Since 20/358 animals from the original Delayed Effects Colony survived after the conclusion of this contract in September 1995, it is hoped that more cataract examinations can be performed on this important group of aging and/or irradiated subjects in the future, at least on an annual basis.

Some cataract data obtained prior to 1985 exists in animal charts and in other records. Included among those records are data from animals which received intermediate and relatively high doses of ionizing radiation as well as early data from monkeys which survived to be examined from 1985 until they died. It will be important to quantify those data not only to fill in blanks in our cataract database prior to 1985, but also to determine the kinetics of early cataract development in control and irradiated monkeys.

Finally, although the contractors were not tasked here to measure DNA damage in monkey retinas, we hope to obtain funding to measure changes in aging and irradiated photoreceptor DNA in order to compare those data with the large data set on DNA damage and repair in aging and irradiated rabbit photoreceptor cells. To that end, we have been freezing retinas in liquid nitrogen and storing them for future DNA measurements using the zonal rotor ultracentrifugation technique developed by the principal investigator at Colorado State University.

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